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(54) NOVEL CYCLIC DEPSIPEPTIDE PF1022 DERIVATIVES

(57) Novel derivatives of PF1022 substance, which are cyclodepsipeptides represented by the general formula (I) shown below or their salts are useful as anthelmintic agent for prevention or treatment of parasitic infections.

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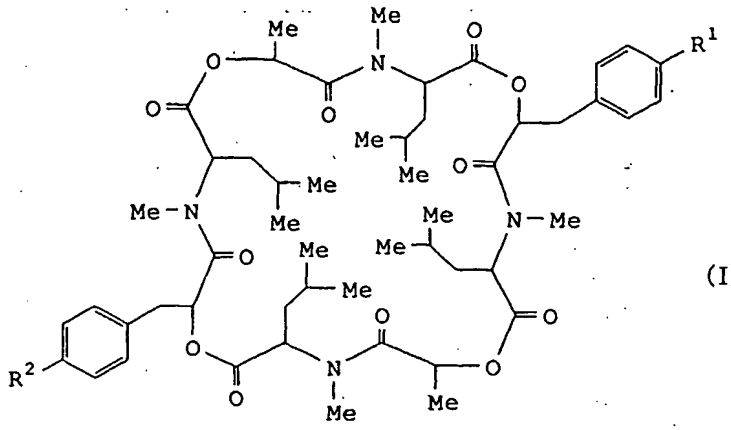


(I)

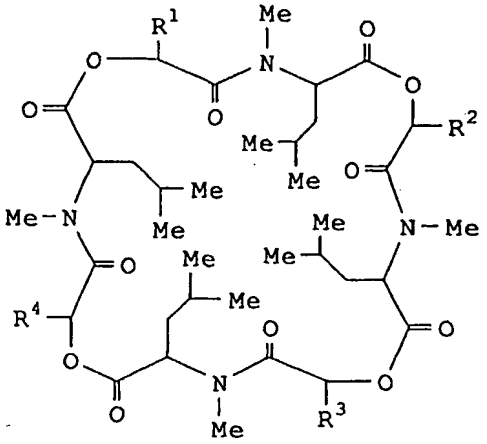
Description

Technical Field

[0001] This invention relates to novel derivatives of PF1022 substance which have a skeletal structure of cyclodepsipeptide same as that of PF1022 substance, that is, a cyclodepsipeptide known as a fermentation product of a microorganism and having an antelmintic activity, and which exhibit a higher anthelmintic activity. This invention also relates to a vermicidal or anthelmintic composition containing said novel PF1022 derivative. The novel PF1022 derivatives according to this invention exhibit an excellent anthelmintic activity capable of expelling a variety of helminths or parasites living in animals and thus are very useful as an anthelmintic agent.

Background Art

[0002] PF1022 substance is a known cyclodepsipeptide which was discovered as a result of studies on anthelmintic substances against fowl roundworms [refer to Japanese patent application Kokai No. Hei 3-35796, European patent application publication No. 0382173A2 and J. Antibiotics, 45, 692, (1992)]. The PF1022 substance is a fermentation product which is produced by the cultivation of a filamentous fungus, PF1022 strain (deposited under FERM BP-2671 with National Institute of Bioscience and Human-Technology Agency in Tsukuba-City in terms of the Budapest Treaty) belonging to Agonomycetales. PF1022 substance is a compound classified into a class of cyclodepsipeptide compounds represented by the following formula (A)



(A)

wherein Me stands for methyl group.

[0003] The cyclodepsipeptide represented by the above formula (A) includes the following eight particular substances.

PF1022 substance : $R^1 = R^3 = Me$, $R^2 = R^4 = CH_2C_6H_5$

PF1022 B substance: $R^1 = R^2 = R^3 = R^4 = CH_2C_6H_5$

PF1022 C substance : $R^1 = Me$, $R^2 = R^3 = R^4 = CH_2C_6H_5$

PF1022 D substance : $R^1 = R^3 = R^4 = Me$, $R^2 = CH_2C_6H_5$

PF1022 E substance : $R^1 = R^3 = Me$, $R^2 = CH_2C_6H_4OH\text{-}p$, $R^4 = CH_2C_6H_5$

PF1022 F substance : $R^1 = R^2 = R^3 = R^4 = Me$

PF1022 G substance : $R^1 = R^2 = R^3 = Me$, $R^4 = CH_2C_6H_4OH\text{-}p$

PF1022 H substance : $R^1 = R^3 = Me$,

$R^2 = R^4 = CH_2C_6H_4OH\text{-}p$

[0004] The PF1022 substance is a cyclodepsipeptide which is formed of L-N-methylleucine [$(CH_3)_2CHCH_2CH(NHCH_3)COOH$] (abbreviated as H-L-MeLeu-OH), D-lactic acid [$CH_3CH(OH)\text{-}COOH$] (abbreviated as H-D-Lac-OH] and D-phenyl-lactic acid [$C_6H_5CH_2CH(OH)COOH$] (abbreviated H-D-PhLac-OH) via ester-bonds and amido-bonds and which may also be represented by the following formula (B):

Formula B: Cyclo (L-MeLeu-D-Lac-L-MeLeu-D-PhLac-L-MeLeu-D-Lac-L-MeLeu-D-PhLac)

[0005] The cultivation of the filamentous fungus PF1022 strain results not only in the production of PF1022 substance as the main product, but also in the production of PF1022 B substance, PF1022 C substance, PF1022 D substance, PF1022 E substance, PF1022F substance, PF1022G substance and PF1022 H substance which have the structures represented in the above formula (A), respectively [see Japanese patent application first publications Kokai Nos. Hei 3-35796, 5-170749 and 6-184126 and Japanese patent application No. Hei 8-208201 (filed on August 7, 1996, not yet laid open)].

[0006] The PF1022 substance and PF1022 B to H substances all possess anthelmintic activities and have specific structural characteristics such that they have a common cyclodepsipeptide structure as a basic skeleton, that they have, as side chains, four N-methyl groups, four isobutyl groups, 0-4 methyl groups, 0-4 benzyl groups and 0-2 p-hydroxybenzyl groups and also that they have eight asymmetric carbon atoms in their molecules. Further, it can be presumed that the presence of a 24-membered ring formed of the four ester-linkages and four amido-linkages as shown in the formula (A) above plays an important role in the expression of biological activities.

[0007] So-called helminthic infections can cause serious dameges to human and animal health and also to agricultural and stock-breeding industries, so that there always exists in the art, as an important theme, a demand for finding and providing such novel and useful substances which exhibit anthelmintic activities.

[0008] As explained above, PF1022 substance was found originally as a fermentation product, and later was prepared by chemical syntheses [see Japanese patent application first publication Kokai No. Hei 5-320148, and Biosci. Biotech. Biochem., 58, 1193 (1994)].

[0009] It is already known that PF1022 substance and PF1022 B to H substances themselves possess very high anthelmintic activities, but some researcher groups are still working in an attempt to produce and find out novel related substance(s) having a higher anthelmintic activity, with utilizing those PF1022 substances as the starting materials.

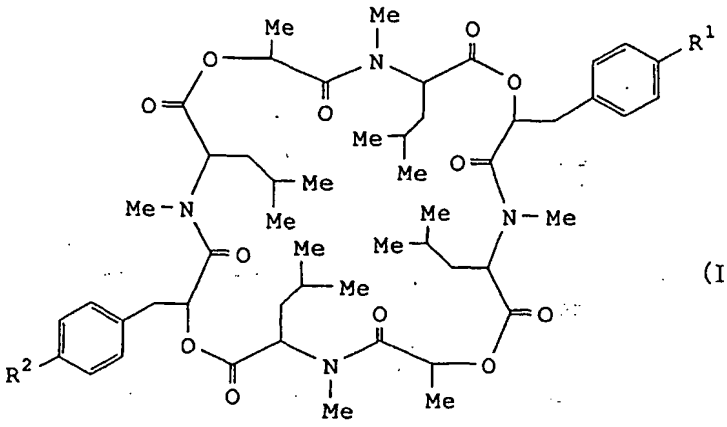
[0010] We, the present inventors, also have proceeded investigations from the initial stage when PF1022 substance was found, in order to produce and find out novel derivatives with starting from PF1022 substance and PF1022 B to H substances, and we have already found several novel derivatives (see internationally published specification No. WO94/19334 of PCT application No. PCT/JP/00252 and European patent application publication No. 0685469 A1 and Japanese patent application No. Hei 7-244051). One of the other researcher groups also has disclosed some novel derivatives as produced by total synthetic processes (see PCT international publications WO93/19033 and No. WO95/07272).

Disclosure of Invention

[0011] As described above, we have carried out our researches and development in an attempt to provide novel derivative(s) having a higher anthelmintic activity than that of PF1022 substance, by means of a method of chemical syntheses using the PF1022 substance as the starting compound. As a result, we have now been able to produce and find out several novel PF1022 derivatives which posesess an anthelmintic activity equal to or higher than that of any known PF1022 related compounds shown in the above-mentioned literatures and specifications.

[0012] Further, we have proceeded our investigations with taking notice of the D-phenyllactic acid moiety as one of the constituents of forming PF1022 substance, and now we have successfully synthesized novel cyclodepsipeptides which may be represented collectively by the undermentioned general formula (I), general formula (II) and general formula (III), through total synthetic processes or through chemical synthetic processes with starting from PF1022 substance, PF1022 E substance and PF1022 H substance. We have found that these novel PF1022 derivatives exhibit strong anthelmintic activities on the basis of animal tests.

[0013] According to a first aspect of this invention, therefore, there is provided a novel cyclodepsipeptide derivative of PF1022 substance, which is represented by the following general formula (I)



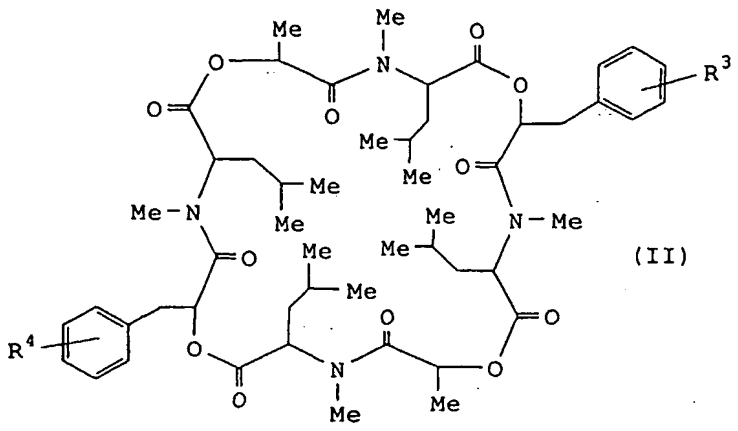
(I)

wherein (i) R^1 stands for a hydrogen atom and R^2 stand for a cyano-(C_1-C_6)alkoxy group, a thiocarbamoyl-(C_1-C_6)alkoxy group, an amino- (C_1-C_6) alkoxy group, an amino- (C_1-C_6) alkoxy group having a protecting group, an N-mono-(C_1-C_6)alkylamino -(C_1-C_6)alkoxy group, an N,N-di-(C_1-C_6)alkylamino-(C_1-C_6) alkoxy group, an N,N-di-((C_1-C_6)alkoxy-(C_1-C_6)alkyl)amino-(C_1-C_6)alkoxy group, or a cyclic amino-(C_1-C_6)alkoxy group of which the cyclic amino group is a 5- or 6-membered ring containing one or more nitrogen atoms and further optionally containing oxygen or sulfur atom(s) as the cyclic amino group -constituting atoms, or a (C_1-C_6)alkoxy group having as a substituent, a saturated or unsaturated 5- or 6-membered heterocyclic ring containing three or less hetero atoms (which is or are nitrogen atom, oxygen atom or sulfur atom) as the heterocyclic ring-constituting atoms and further optionally having as a substituent a phenyl group which may optionally be substituted by a (C_1-C_6)alkyl group, a (C_3-C_6)cycloalkyl group or a halogen atom (chlorine, bromine or fluorine), or a (C_2-C_6)alkanoyl group optionally having a substituent (which is a halogen atom or hydroxyl group), or an N-mono-(C_1-C_6)alkylcarbamoyl group, or an N,N-di-(C_1-C_6)alkylcarbamoyl group, or a cyclic amino-carbonyl group of which the cyclic amino group is a 5- or 6-membered ring containing one or more nitrogen atoms and further optionally containing oxygen or sulfur atom(s) as the cyclic amino group-constituting atoms, or an N-mono-(C_1-C_6) alkylamino-alkoxycarbonyl group, or an N,N-di-(C_1-C_6) alkylamino-(C_1-C_6)alkoxycarbonyl group , or a cyclic amino - (C_1-C_6) alkoxycarbonyl group of which the cyclic amino group is a 5- or 6-membered ring containing one or more nitrogen atoms and further optionally containing oxygen or sulfur atom(s) as the cyclic amino group-constituting atoms, or a formyloxy-(C_1-C_6)alkylcarbonyl group, or a carboxyl group, t-butyl group, 2-aminothiazolyl group, or t-butoxy group; or alternatively (ii) R^1 and R^2 are identical to each other and each stand for a cyano-(C_1-C_6)alkoxy group, a thiocarbamoyl-(C_1-C_6)alkoxy group, an amino-(C_1-C_6)alkoxy group, an amino-(C_1-C_6)alkoxy group having a protecting group, an N-mono-(C_1-C_6)alkylamino-(C_1-C_6)alkoxy group, an N,N-di (C_1-C_6)alkylamino-(C_1-C_6)alkoxy group, an N,N-di-((C_1-C_6) alkoxy-(C_1-C_6)alkyl)amino-(C_1-C_6)alkoxy group, or a cyclic amino- (C_1-C_6) alkoxy group of which the cyclic amino group is a 5- or 6-membered ring containing one or more nitrogen atoms and further optionally containing oxygen or sulfur atom(s) as the cyclic amino group-constituting atoms, or a (C_1-C_6) alkoxy group having as a substituent a saturated or unsaturated 5- or 6-membered heterocyclic ring containing three or less hetero atoms (which is or are nitrogen atom, oxygen atom or sulfur atom) as the heterocyclic ring-constituting atoms and further optionally having as a substituent a phenyl group which may optionally be substituted by a (C_1-C_6)alkyl group, a (C_3-C_6)cycloalkyl group or a halogen atom (chlorine, bromine or fluorine), or a (C_2-C_6)alkanoyl group optionally having a substituent (which is a halogen atom or hydroxyl group), or an N-mono-(C_1-C_6)alkylcarbamoyl group, or an N,N-di-(C_1-C_6) alkylcarbamoyl group, or a cyclic amino-carbonyl group of which the cyclic amino group is a 5- or 6-membered ring containing one or more nitrogen atoms and further optionally containing oxygen or sulfur atom(s) as the cyclic amino group-constituting atoms, or an N-mono-(C_1-C_6)alkylamino-(C_1-C_6) alkoxycarbonyl group, or an N,N-di-(C_1-C_6)alkylamino-(C_1-C_6)alkoxycarbonyl group, or a cyclic amino-(C_1-C_6) alkoxycarbonyl group of which the cyclic amino group is a 5- or 6-membered ring containing one or more nitrogen atoms and further optionally containing oxygen or sulfur atom(s) as the cyclic amino group-constituting atoms, or a formyloxy(C_1-C_6)alkylcarbonyl group, or a carboxyl group, t-butyl group, 2-aminothiazolyl group or t-butoxy group, and Me stands for methyl group.

[0014] In general formula (I) above, where R^1 or R^2 stands for such a cyclic amino-(C_1-C_6)alkoxy group, cyclic amino-carbonyl group or cyclic amino-(C_1-C_6)alkoxycarbonyl group of which the cyclic amino group is a 5- or 6-membered ring containing one or more nitrogen atoms and further optionally containing oxygen or sulfur atom(s) as the cyclic amimo group-constituting atoms, some preferred examples of the cyclic amino group contained in the aforesaid groups are

morpholino group, pyrrolidino group and piperidino group. Further, in general formula (I) above, where R^1 or R^2 stands for a (C_1-C_6)alkoxy group having a saturated or unsaturated 5- or 6-membered heterocyclic ring as a substituent, some preferred examples of said heterocyclic ring are pyrrolidine, imidazole, thiazole, furan, tetrahydrofuran, a 5-(C_1-C_6) alkyl-1,2,4-oxadiazole, a 5- (halo-substituted or unsubstituted) phenyl-1, 2,4-oxadiazole, a 5-(C_1-C_6) cycloalkyl-1,2,4-oxadiazole, a halo-substituted or unsubstituted pyridine, and an N-alkyl-substituted or unsubstituted tetrahydropyrimidine.

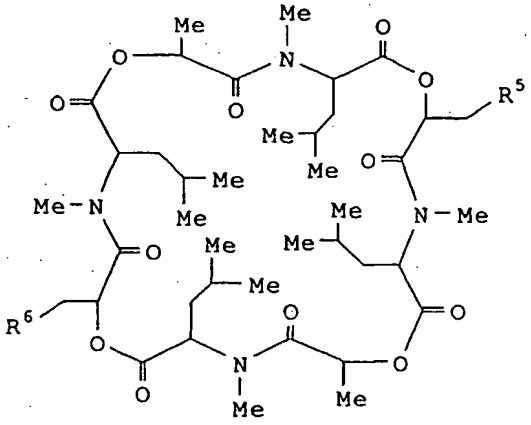
[0015] According to a second aspect of this invention, there is provided a cyclodepsipeptide derivative of PF1022 substance, which is represented by the following general formula (II)



(II)

wherein (i) R^3 stands for a hydrogen atom and R^4 stands for a morpholino group bonded to any of the ortho-, meta- and para- position of the phenyl group shown in the above formula; or alternatively (ii) R^3 stands for a morpholino group bonded to any of the ortho-, meta- and para-positions of the phenyl group shown in the above formula and R^4 stands for a morpholino group bonded to the ortho- or meta-position of the phenyl group and Me stands for methyl group.

[0016] Further, according to a third aspect of this invention, there is provided a cyclodepsipeptide derivative of PF1022 substance, which is represented by the following general formula (III)



(III)

[0017] wherein (i) R^6 stands for a phenyl group and R^5 stands for a carboxyl group, a protected carboxyl group, a (C_1-C_6) alkoxycarbonyl group, an unsaturated 5- or 6-membered heterocyclic ring containing one or more nitrogen, oxygen or sulfur atoms as the hetero atom of said ring, or a bicyclic fused heterocyclic ring as formed by fusion of said unsaturated 5- or 6-membered heterocyclic ring with a benzene ring, or alternatively (ii) R^5 and R^6 are identical to each other and each stand for a carboxyl group, a protected carboxyl group, a (C_1-C_6)alkoxycarbonyl group, or an unsaturated 5-

or 6-membered heterocyclic ring containing one or more nitrogen, oxygen or sulfur atoms as the hetero atom of said ring, or a bicyclic fused heterocyclic ring as formed by fusion of said unsaturated 5- or 6-membered heterocyclic ring with a benzene ring, and Me stands for methyl group.

[0018] In general formula (III) above, where R^5 or R^6 stands for an unsaturated 5- or 6-membered heterocyclic ring or a bicyclic fused heterocyclic ring as formed by fusion of said unsatutated heterocyclic ring with a benzene ring, some preferred examples of the heterocyclic ring or fused ring are benzothiazolyl group, benzimidazolyl group and 2-amino-thiazolyl group.

Best Mode for Carrying Out the Invention

[0019] A preferred embodiment of the novel derivative of PF1022 substance of the general formula (I) according to the first aspect of this invention can be a cyclodepsipeptide of general formula (I) wherein R^1 is a hydrogen atom and R^2 is a cyanomethoxy group, thiocarbamolymethoxy group, 2-aminoethoxy group, 2-(N-t-butyloxycarbonylamino)ethoxy group, a 2-(N-mono-(C_1-C_6)alkylamino)ethoxy or 3-(N-mono-(C_1-C_6)alkylamino)propoxy group, a 2-(N,N-di-(C_1-C_6) alkylamino)ethoxy or 3-(N,N-di-(C_1-C_6)alkylamino)propoxy group, a 2-(N,N-di-(C_1-C_6)alkoxy-(C_1-C_6)alkyl)amino)-ethoxygroup, 2-morpholinoethoxygroup, 2-pyrrolidinoethoxy group, 2-piperidinoethoxy group, or a methoxy group substituted by a heterocyclic ring which is pyrrolidine, imidazole, thiazole, furan, tetrahydrofuran, a 5- (linear or branched C_1-C_6)alkyl-1,2,4-oxadiazole, a 5-(optionally halo-substituted)phenyl-1,2,4-oxadiazole, a 5-(C_3-C_6) cycloalkyl-1,2,4-oxadiazole, a pyridine optionally substituted by a halogen atom, or an N-((C_1-C_6) alkyltetrahydropyrimidine, or R^2 is an acetyl group optionally substituted by a substituent (a halogen atom or hydroxyl group), or a carbamoyl group, N-methylcarbamoyl group, N,N-dimethylcarbamoyl group, morpholinocarbonyl group, an N-mono-(C_1-C_6)alkylaminoethoxy-carbonyl group, an N,N-di-(C_1-C_6)alkylaminoethoxycarbonyl group, morpholinoethoxycarbonyl group, formyloxymethylcarbonyl group, carboxyl group, t-butyl group, 2-aminothiazolyl group or t-butoxy group; or alternatively (ii) R^1 and R^2 are identical to each other and each are a cyanomethoxy group, thiocarbamoylmethoxy group, 2-aminoethoxy group, 2-(N-t-butyloxycarbonylamino)ethoxy group, a 2-(N-mono-(C_1-C_6) alkylamino)ethoxy or 3-(N-mono-(C_1-C_6)alkylamino)propoxy group, a 2-(N,N-di-(C_1-C_6)alkylamino)ethoxy or 3-(N,N-di (C_1-C_6)alkylamino)propoxygroup, a 2-(N,N-di-(C_1-C_6)alkoxy-(C_1-C_6)alkylamino)ethoxy group, 2-morpholinoethoxy group, 2-pyrrolidinoethoxy group, 2-piperidinoethoxy group, or a methoxy group substituted by a heterocyclic ring which is pyrrolidine, imidazole, thiazole, furan, tetrahydrofuran, a 5- (linear or branched C_1-C_6)alkyl-1,2,4-oxadiazole, a 5-(optionally halo-substituted)phenyl-1,2,4-oxadiazole, a 5-(C_3-C_6)cycloalkyl-1,2,4-oxadiazole, a pyridine optionally substituted by a halogen atom, or an N-(C_1-C_6)alkyl-tetrahydropyrimidine, or R^1 and R^2 are each an acetyl group optionally substituted by a substituent (a halogen atom or hydroxyl group), or a carbamoyl group, N-methylcarbamoyl group, N,N-dimethylcarbamoyl group, morpholinocarbonyl group, an N-mono- (C_1-C_6) alkylamino-ethoxycarbonyl group, an N,N-di-(C_1-C_6)alkylamino-ethoxycarbonyl group, morpholinoethoxycarbonyl group, formyloxymethylcarbonyl group, carboxyl group, t-butyl group, 2-aminothiazolyl group or t-butoxy group.

[0020] The cyclodepsipeptide derivative of general formula (I) according to the first aspect of this invention includes, as its preferred embodiments, the compounds of the following classes (a) to (c).

(a) Cyclodepsipeptide of general formula (I) wherein (i) R^1 is a hydrogen atom, and R^2 is a cyano-(C_1-C_6)alkoxy group, a thiocarbamoyl-(C_1-C_6)alkoxy group, an amino(C_1-C_6)alkoxy group, an amino-(C_1-C_6)alkoxy group having a protecting group, an N-mono-(C_1-C_6)alkylamino-(C_1-C_6) alkoxy group, an N,N-di-((C_1-C_6)alkylamino-(C_1-C_6)alkoxy group, an N,N-di-((C_1-C_6) alkoxy-(C_1-C_6)alkyl)amino-(C_1-C_6) alkoxy group, or a cyclic amino- (C_1-C_6) alkoxy group of which the cyclic amino group is a 5- or 6-membered ring containing one or more nitrogen atoms and further optionally containing oxygen atom or sulfur atom as the cyclic amino groupconstituting atoms, or R^2 is t-butoxy group; or alternatively (ii) R^1 and R^2 are identical to each other and each are a cyano-(C_1-C_6)alkoxy group, a thiocarbamoyl-(C_1-C_6)alkoxy group, an amino-(C_1-C_6)alkoxy group, an amino-(C_1-C_6)alkoxy group having a protecting group, an N-mono-(C_1-C_6)alkylamino -(C_1-C_6)alkoxy group, an N,N-di-(C_1-C_6)alkylamino-(C_1-C_6) alkoxy group, an N, N-di- ((C_1-C_6) alkoxy- (C_1-C_6) alkyl) amino(C_1-C_6)alkoxy group, or a cyclic amino-(C_1-C_6)alkoxy group of which the cyclic amino group is a 5- or 6-membered ring containing one or more nitrogen atoms and further optionally containing oxygen atom or sulfur atom as the cyclic amino group-constituting atoms, or R^1 and R^2 are each t-butoxy group.

In the cyclodepsipeptide just above-mentioned, it is preferable that (i) R^1 is a hydrogen atom and R^2 is a cyanomethoxy group, thiocarbamoylmethoxy group, a 2-aminoethoxy group, 2-(N-t-butyloxycarbonylamino)ethoxy group, a 2-(N-mono-(C_1-C_6)alkylamino)ethoxy or 3-(N-mono-(C_1-C_6)alkylamino)propoxy group, a 2-(N,N-di-(C_1-C_6) alkylamino)ethoxy or 3-(N,N-di-(C_1-C_6)alkylamino)propoxy group, a 2-(N,N-di-((C_1-C_6)alkoxy-(C_1-C_6)alkyl)amino) ethoxy group, 2-morpholinoethoxy group, 2-pyrrolidinoethoxy group or 2-piperidinoethoxy group or t-butoxy group ; or alternatively that (ii) R^1 and R^2 are the same with each other and each are a cyanomethoxy group, 2-aminoethoxy group , 2-(N-t-butyloxycarbonylamino)ethoxy group, a 2-(N-mono-(C_1-C_6)-alkylamino)ethoxy

or 3-(N-mono-(C_1-C_6)alkylamino) propoxy group, a 2-(N,N-di-(C_1-C_6)alkylamino)ethoxy or 3-(N,N-di-(C_1-C_6)alkylamino)propoxy group, a 2-(N,N-di-((C_1-C_6)alkoxy-(C_1-C_6)alkyl)amino)ethoxy group, 2-morpholinoethoxy group, 2-pyrrolidinoethoxy group or 2-piperidinoethoxy group, or t-butoxy group.

(b) Cyclodepsipeptide of general formula (I) wherein R^1 is a hydrogen atom, and R^2 is a (C_1-C_6) alkoxy group having, as a substituent, such a saturated or unsaturated 5- or 6-membered heterocyclic ring which contains three or less hetero atoms (being nitrogen, oxygen or sulfur atoms) as the heterocyclic ring -constituting atoms and which may optionally have as a substituent a (C_1-C_6)alkyl group or a (C_3-C_6)cycloalkyl group or a phenyl group optionally substituted by a halogen atom; or alternatively (ii) R^1 and R^2 are each independently a (C_1-C_6)alkoxy group having as a substituent such a saturated or unsaturated 5- or 6-membered heterocyclic ring which contains three or less hetero atoms (being nitrogen, oxygen or sulfur atoms) as the heterocyclic ring-constituting atoms and which may optionally have as a substituent a (C_1-C_6)alkyl group or a (C_3-C_6)cycloalkyl group or a phenyl group optionally substituted by a halogen atom.

In the cyclodepsipeptide just above-mentioned, the heterocyclic ring, which is referred to for the (C_1-C_6)alkoxy group having as a substituent a heterocyclic ring as represented by R^1 and/or R^2, may be a pyrrolidine, imidazole, thiazole, furan, tetrahydrofuran, a 5-(C_1-C_6, linear or branched)alkyl-1,2,4-oxadiazole, a 5-(optionally halo-substituted)-phenyl-1,2,4-oxadiazole, a 5-(C_3-C_6) cycloalkyl-1,2,4-oxadiazole, a pyridine optionally substituted by a halogen, or an N-(C_1-C_6)alkyl-tetrahydropyrimidene. Further, R^2, or both of R^1 and R^2 may be a methoxy group which is substituted by such specific heterocyclic ring as above-mentioned.

(c) Cyclodepsipeptide of general formula (I) wherein R^1 is a hydrogen atom, and R^2 is a (C_2-C_6)alkanoyl group optionally substituted by a halogen atom or hydroxy group as s substituent, or an N-mono-(C_1-C_6)alkylcarbamoyl group, an N,N-di-(C_1-C_6)alkylcarbamoyl group, a cyclic aminocarbonyl group of which the cyclic amino group is a 5- or 6-membered ring containing one or more nitrogen atoms and further optionally containing oxygen or sulfur atom(s) as the cyclic amino group-constituting atoms, an N-mono(C_1-C_6)alkylamino-alkoxycarbonyl group, an N,N-di-(C_1-C_6) alkylamino-alkoxycarbonyl group, a cyclic amino-(C_1-C_6) alkoxycarbonyl group of which the cyclic amino group is a 5- or 6-membered ring containing one or more nitrogen atoms and further optionally containing oxygen or sulfur atom(s) as the cyclic amino group-constituting atoms, a formyloxy(C_1-C_6)alkylcarbonyl group, carboxyl group, t-butyl group, or 2-aminothiazolyl group; or alternatively (ii) R^1 and R^2 are identical to each other and each are a (C_2-C_6)alkanoyl group optionally substituted by a halogen atom or hydroxyl group as a substituent, or an N-mono-(C_1-C_6)alkylcarbamoyl group, an N,N-di-(C_1-C_6)alkylcarbamoyl group, a cyclic amino-carbonyl group of which the cyclic amino group is a 5- or 6-membered ring containing one or more nitrogen atoms and further optionally containing oxygen or sulfur atom(s) as the cyclic amino group-constituting atoms, an N-mono-(C_1-C_6)alkylamino-alkoxycarbonyl group, an N,N-di-(C_1-C_6) alkylamino-alkoxycarbonyl group, a cyclic amino-(C_1-C_6)-alkoxycarbonyl group of which the cyclic amino group is a 5- or 6-membered ring containing one or more nitrogen atoms and further optionally containing oxygen or sulfur atom(s) as the cyclic amino group-constituting atoms, a formyloxy-(C_1-C_6)alkylcarbonyl group, carboxyl group, t-butyl group, or 2-aminothiazolyl group.

[0021] In the cyclodepsipeptides referred to just above, it is preferable that (i) R^1 is a hydrogen atom and R^2 is a carboxyl group, an acetyl group optionally substituted by a halogen atom or hydroxyl group as a substituent, a carbamoyl group, N-methylcarbamoyl group, an N,N-dimethylcarbamoyl group, morpholinocarbonyl group, an N-mono-(C_1-C_6) alkylamino-ethoxycarbonyl group, an N,N-di-(C_1-C_6) alkylamino-ethoxycarbonyl group, morpholinoethoxycarbonyl group or formyloxymethoxycarbonyl group; or alternatively (ii) R^1 and R^2 are identical to each other and each are a carboxyl group, an acetyl group optionally substituted by a halogen atom or hydroxyl group as a substituent, a carbamoyl group, an N-methylcarbamoyl group, an N,N-dimethylcarbamoyl group, a morpholinocarbonyl group, an N-mono-(C_1-C_6) alkylamino-ethoxycarbonyl group, an N,N-di-(C_1-C_6) alkylamino-ethoxycarbonyl group, a morpholinoethoxycarbonyl group or formyloxymethoxycarbonyl group.

[0022] According to a preferred embodiment of the cyclodepsipeptide of general formula (II) in the second aspect of this invention, there are exemplified such a cyclodepsipeptide of general formula (II) wherein (i) R^3 is a hydrogen atom and R^4 is a morpholino group bonded to the para- position of the phenyl group shown in the formula, or alternatively (ii) R^3 is a morpholino group bonded to the ortho- or para-position of the phenyl group and R^4 is a morpholino group bonded to the ortho-position of the phenyl group.

[0023] According to a preferred embodiment of the cyclodepsipeptides of general formula (III) in the third aspect of this invention, there are exemplified such a cyclodepsipeptide of general formula (III) wherein (i) R^6 is a phenyl group and R^5 is a carboxyl group, methoxycarbonyl group, diphenylmethoxycarbonyl group, benzothiazolyl group or benzimidazolyl group, or alternatively (ii) R^5 and R^6 are identical to each other and each are a carboxyl group, methoxycarbonyl group, diphenylmethoxycarbonyl group, benzothiazolyl group or benzimidazolyl group.

[0024] Concrete examples of the cyclodepslipeptide of general formula (I) according to the first aspect of this invention include such compounds which are produced by Examples 4-46, 49-64, 67-68 and 72 given hereinafter. As concrete examples of the cyclodepsipeptide of general formula (II) according to the second aspect of this invention, there are

such compounds which are produced by Examples 65-66 shown hereinafter. Further, as concrete examples of the cyclodepsipeptide of general formula (III) according to the third aspect of this invention, there are such compounds which are produced by Examples 47-48, 69, 70 and 71 given hereinafter.

[0025] Amongst the cycdepsipeptides of general formula (I), general formula (II) and general formula (III) according to this invention, the particular compounds of the following Examples are especially preferred.

Example 4. Cyclo[MeLeu-Lac-MeLeu-(NCCH$_2$O)PhLac-MeLeu-Lac -MeLeu-PhLac]
Example 5. Cyclo[MeLeu-Lac-MeLeu-(BocNHCH$_2$CH$_2$O)PhLac-MeLeu-Lac-MeLeu-PhLac]
Example 6. Cyclo[MeLeu-Lac-MeLeu-(NH$_2$CH$_2$CH$_2$O)PhLac-MeLeu -Lac-MeLeu-PhLac] (Compound Code No. PF1022-278)
Example 7. Cyclo[MeLeu-Lac-MeLeu-((CH$_3$)$_2$NCH$_2$CH$_2$O)PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-235)
Example 8. Cyclo[MeLeu-Lac-MeLeu-((C$_2$H$_5$)$_2$NCH$_2$CH$_2$O)PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-236)
Example 9. Cyclo[MeLeu-Lac-MeLeu-(Pr$_2$NCH$_2$CH$_2$O)PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-270)
Example 10. Cyclo[MeLeu-Lac-MeLeu-(Bu$_2$NCH$_2$CH$_2$O)PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-271)
Example 11. Cyclo[MeLeu-((CH$_3$OCH$_2$CH$_2$)$_2$NCH$_2$CH$_2$O)PhLac-MeLeu -Lac-MeLeu-PhLac-MeLeu-Lac] (Compound Code No. PF1022-238)
Example 12. Cyclo[MeLeu-(MorCH$_2$CH$_2$O)PhLac-MeLeu-Lac-MeLeu -PhLac-MeLeu-Lac] (PF1022-239)
Example 13. Cyclo[MeLeu-Lac-MeLeu-(PyrCH$_2$CH$_2$O)PhLac-MeLeu -Lac-MeLeu-PhLac] (Compound Code No. PF1022-284)
Example 14. Cyclo[MeLeu-Lac-MeLeu-(pipCH$_2$CH$_2$O)PhLac-MeLeu -Lac-MeLeu-PhLac] (Compound Code No. PF1022-285)
Example 15. Cyclo[MeLeu-Lac-MeLeu-((C$_2$H$_5$)$_2$NCH$_2$CH$_2$CH$_2$O) PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-274)
Example 16. Cyclo[MeLeu-Lac-MeLeu-((S)-pyrrolidinyl-2-methoxy)PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-302)
Example 17. Cyclo[MeLeu-Lac-MeLeu-(4-imidazolyl-4-methoxy)PhLac-MeLeu-Lac-MeLeu-PhLac] (PF1022-304)
Example 18. Cyclo[MeLeu-Lac-MeLeu-(H$_2$NCSCH$_2$O)PhLac-MeLeu-Lac-MeLeu-PhLac]
Example 19. Cyclo[MeLeu-Lac-MeLeu-(2-imidazolylmethoxy) PhLac-MeLeu-Lac-MeLeu-PhLac] (PF1022-305)
Example 20. Cyclo[MeLeu-Lac-MeLeu-(2-thiazolylmethoxy) PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-306)
Example 21. Cyclo[MeLeu-Lac-MeLeu-(3-(5-methyl-1,2,4-oxadiazolyl)-methoxy)PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-309)
Example 22. Cyclo[MeLeu-Lac-MeLeu-(3-(5-isobutyl-1,2,4-oxadiasolyl)methoxy)PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-310)
Example 23. Cyclo[MeLeu-Lac-MeLeu-(3-(5-(2,6-difluorophenyl) -1,2, 4-oxadiazolyl) methoxy) PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-311)
Example 24. Cyclo[MeLeu-Lac-MeLeu-(furfuryloxy)PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-312)
Example 25. Cyclo[MeLeu-Lac-MeLeu-(tetrahydrofurfuryloxy) PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-313)
Example 26. Cyclo[MeLeu-Lac-MeLeu-(2-picolyloxy)PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-314)
Example 27. Cyclo[MeLeu-Lac-MeLeu-(3-picolyl)PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-315)
Example 28. Cyclo[MeLeu-Lac-MeLeu-(4-picolyl)PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-316)
Example 29. Cyclo[MeLeu-Lac-MeLeu-(6-chloro-3-picolyloxy) PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-317)
Example 30. Cyclo[MeLeu-Lac-MeLeu-(2-(1N-methyl-1,4,5,6-tetrahydropyrimidyl) methoxy) PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-318)
Example 31. Cyclo[MeLeu-Lac-MeLeu-(3-(5-isopropyl-1,2,4-oxadiazolyl) -methoxy) PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-341)
Example 32. Cyclo[MeLeu-Lac-MeLeu-(3-(5-cyclohexyl-1,2,4-oxadiazolyl) -methoxy) PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-343)

Example 33. Cyclo[MeLeu-Lac-MeLeu-(NCCH$_2$O)PhLac]$_2$

Example 34. Cyclo[MeLeu-Lac-MeLeu-(BocNHCH$_2$CH$_2$O)PhLac]$_2$

Example 36. Cyclo[MeLeu-Lac-MeLeu-((CH$_3$)$_2$NCH$_2$CH$_2$O)PhLac]$_2$ (Compound Code No. PF1022-262)

Example 37. Cyclo[MeLeu-Lac-MeLeu-((C$_2$H$_5$)$_2$NHCH$_2$H$_2$O)PhLac]$_2$ (Compound Code No. PF1022-263)

Example 38. Cyclo[MeLeu-Lac-MeLeu-(MorCH$_2$H$_2$O)PhLac]$_2$ (Compound Code No. PF1022-266)

Example 39. Cyclo[MeLeu-Lac-MeLeu-(3-(5-isobutyl-1,2,4-oxadiazolylmethoxy)PhLac]$_2$ (Compound Code No. PF1022-330)

Example 40. Cyclo[MeLeu-Lac-MeLeu-(3-(5-(2,6-difluorophenyl) -1,2, 4-oxadiazolyl)methoxy) PhLac]$_2$ (Compound Code No. PF1022-331)

Example 41. Cyclo[MeLeu-Lac-MeLeu-(tetrahydrofurfuryloxy) PhLac]$_2$ (Compound Code No. PF1022-333)

Example 42. Cyclo[MeLeu-Lac-MeLeu-(2-picolyloxy)PhLac]$_2$ (Compound Code No. PF1022-334)

Example 43. Cyclo[MeLeu-Lac-MeLeu-(3-(5-isopropyl-1,2,4-oxadiazolyl)-methoxy)PhLac]$_2$ (Compound Code No. PF1022-345)

Example 44. Cyclo[MeLeu-Lac-MeLeu-(3-(5-cyclohexyl-1,2,4-oxadiazolyl)-methoxy)PhLac]$_2$ (Compound Code No. PF1022-347)

Example 45. Cyclo[MeLeu-Lac-MeLeu-PhLac-MeLeu-Lac-MeLeu-(NH$_2$CO)PhLac] (Compound Code No. PF1022-242)

Example 46. Cyclo[MeLeu-Lac-MeLeu-(NH$_2$CO)PhLac]$_2$(Compound Code No. PF1022-247)

Example 47. Cyclo[MeLeu-Lac-MeLeu-(HOCO)Lac]$_2$ (Compound Code No. PF1022-030) and Cyclo[MeLeu-Lac-MeLeu-(HOCO)Lac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-031)

Example 48. Cyclo[MeLeu-Lac-MeLeu-((C$_6$H$_5$)$_2$CHOCO)Lac]$_2$ (Compound Code No. PF1022-045) and Cyclo[MeLeu-Lac-MeLeu-(C$_6$H$_5$)$_2$CHOCO)Lac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-046)

Example 49. Cyclo[MeLeu-Lac-MeLeu-(CH$_3$CO)PhLac-MeLeu-Lac-MeLeu-PhLac] and Cyclo[MeLeu-Lac-MeLeu-(CH$_3$CO)PhLac-MeLeu-Lac-MeLeu-(CH$_3$CO)PhLac] (Compound Code No. PF1022-049 and PF1022-048)

Example 50. Cyclo[MeLeu-Lac-MeLeu-(BrCH$_2$CO)PhLac-MeLeu-Lac-MeLeu-PhLac]

Example 51. Cyclo[MeLeu-Lac-MeLeu-(HCOOCH$_2$CO)PhLac-MeLeu-Lac-MeLeu-PhLac]

Example 52. Cyclo[MeLeu-Lac-MeLeu-(HOCH$_2$CO)PhLac-MeLeu-Lac-MeLeu-PhLac]

Example 53. Cyclo[MeLeu-Lac-MeLeu-(HOCO)PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-241)

Example 54. Cyclo[MeLeu-Lac-MeLeu-(MorCO)PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-244)

Example 55. Cyclo[MeLeu-Lac-MeLeu-((CH$_3$)$_2$NCO)PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-243)

Example 56. Cyclo[MeLeu-Lac-MeLeu-((CH$_3$)$_2$NCH$_2$CH$_2$OCO)PhLac- MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-245)

Example 57. Cyclo[MeLeu-Lac-MeLeu-(MorCH$_2$CH$_2$OCO)PhLac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-246)

Example 58. Cyclo[MeLeu-Lac-MeLeu-(BrCH$_2$CO)PhLac]$_2$

Example 59. Cyclo[MeLeu-Lac-MeLeu-(HCOOCH$_2$CO)PhLac]$_2$

Example 60. Cyclo[MeLeu-Lac-MeLeu-(HOCH$_2$CO)PhLac]$_2$

Example 61. Cyclo[MeLeu-Lac-MeLeu-(HOCO)PhLac]$_2$

Example 62. Cyclo[MeLeu-Lac-MeLeu-((CH$_3$)$_2$NCO)PhLac]$_2$ (Compound Code No. PF1022-248)

Example 63. Cyclo[MeLeu-Lac-MeLeu-(MorCO)PhLac]$_2$(Compound Code No. PF1022-249)

Example 64. Cyclo[MeLeu-Lac-MeLeu-(MorCH$_2$CH$_2$OCO)PhLac]$_2$ (Compound Code No. PF1022-251)

Example 65. Cyclo[MeLeu-(Mor)PhLac-MeLeu-Lac-MeLeu-PhLac-MeLeu-Lac] (Compound Code No. PF1022-233)

Example 66. Cyclo[MeLeu-(o-Mor)PhLac-MeLeu-Lac-MeLeu-(p-Mor)PhLac-MeLeu-Lac] (Compound Code No. PF1022-280) and Cyclo[MeLeu-(o-Mor)PhLac-MeLeu-Lac]$_2$(Compound Code No. PF1022-281)

Example 67. Cyclo[MeLeu-Lac-MeLeu-(t-Bu)PhLac-MeLeu-Lac-MeLeu-PhLac] and Cyclo[MeLeu-Lac-MeLeu-(t-Bu)PhLac]$_2$ (Compound Code No. PF1022-051 and PF1022-050)

Example 68. Cyclo[MeLeu-Lac-MeLeu-(t-BuO)PhLac]$_2$(Compound Code No. PF1022-222)

Example 69. Cyclo[MeLeu-Lac-MeLeu-(BTH)Lac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-038)

Example 70. Cyclo[MeLeu-Lac-MeLeu-(BTH)Lac]$_2$(Compound Code No. PF1022-037)

Example 71. Cyclo[MeLeu-Lac-MeLeu-(BIM)Lac-MeLeu-Lac-MeLeu-PhLac] (Compound Code No. PF1022-040)

Example 72. Cyclo[MeLeu-Lac-MeLeu-(ATH)PhLac]$_2$ (Compound Code No. PF1022-056).

[0026] Referring to the above list of Examples, the substances of Examples 4-46, 49-64, 67, 68 and 72 are examples of the compounds of general formula (I), the substances of Examples 65 and 66 are examples of the compounds of

general formula (II), and the substances of Examples 47, 48 and 69-71 are examples of the compounds of general formula (III).

(I) Next, processes for the preparation of the new derivatives of PF1022 substance of general formula (I) according to this invention are explained.

1. Processes comprising the chemical conversion of PF1022 E substance

[0027] The known PF1022 E substance, namely such compound of general formula (I) wherein R^1 is hydrogen atom and R^2 is hydroxyl group, may be used as the starting naterial in the below-described processes in order to synthesize such compounds of general formula (I) where R^1 is hydrogen atom and R^2 is a cyano-(C_1-C_6)alkoxy group, thiocarbamoyl-(C_1-C_6)alkoxy group, amino-(C_1-C_6)alkoxy group, amino(C_1-C_6)alkoxy group having a protecting group, N-mono-(C_1-C_6)alkylamino-(C_1-C_6)alkoxy group, N,N-di-((C_1-C_6) alkoxy-(C_1-C_6)alkyl)amino-(C_1-C_6)alkoxy group, or a cyclic amino- (C_1-C_6) alkoxy group of which the cyclic amino group is a 5- or 6-membered ring containing one or more nitrogen atoms and further optionally containing oxygen atom or sulfur atom as the cyclic amino group-constituting atoms, or a (C_1-C_6) alkoxy group having as a substituent such a saturated or unsaturated 5- or 6 membered heterocyclic ring which contains three or less hetero atoms (nitrogen, oxygen or sulfur atoms) as the heterocyclic ring-constituting atoms and which may have a substituent (being a C_1-C_6-alkyl group or a C_3-C_6-cycloalkyl group or a phenyl group optionally substituted by a halogen atom), or R^2 is t-butoxy group.

[0028] PF1022 E substance may be obtained from the culture broth of the PF1022 substance-producing strain by a fermentation process and by itself has an anthelmintic activity against worms parasitic on animals. We have paid attention on that the possibility of chemical modification of PF1022 E substance would have been extended due to the presence of a phenolic hydroxyl group at the para-position of one of the two benzene rings in the molecule of PF1022 E substance. And thus, we can have synthesized the novel derivative according to this invention, by applying various chemical conversion procedures to the PF1022 E substance. PF1022 E substance itself may also be synthesized from PF1022 substance by the following method:

1-1. Syntheses of PF1022 E substance from PF1022 substance

[0029] PF1022 E substance can be produced either by a fermentation process (see Japanese patent application first publication Kokai Hei-6-184126), or by a synthetic process (see PCT International Publication No.W094/19334), as above-mentioned. PF1022 E substance may also be synthesized from PF1022 substance through a method comprising four step chemical reactions. In the latter 4-step synthetic method, PF1022 E substance can be prepared by the method comprising the first step for nitration of the hydroxyl group at the para-position of the benzene ring of PF1022 substance, the second step for reduction of the nitro group into an amino group, the third step for diazotization of the amino group, and the fourth step for hydrolysis of the diazonium salt. The above first step to the fourth step of this synthetic method are now detailed below.

[The first step]

[0030] It is well known that, in general, a mixture of concentrated sulfuric acid (or sulfur trioxide) with concentrated nitric acid, or fuming nitric acid alone, and the like is used as a useful reagent for such nitration of hydrogen atom(s) present on benzene ring, which is effected by electrophilic substitution reaction. However, we have already found that, so far as the nitration of PF1022 substance is concerned, it is difficult to introduce a nitro group into only one of the two benzene rings of PF1022 substance and specially at the para-position of the benzene ring with a high selectivity, because PF1022 substance has the two benzene rings which are chemically equivalent to each other.

[0031] We have studied on a variety of reagents and reaction conditions, and thus we have now succeeded in achieving the nitration of the phenolic hydroxyl group present at the para-position of the phenyl group of PF1022 substance by a process comprising dissolving the PF1022 substance in acetic anhydride, followed by reacting it with a stoichiometrically specified amount of fuming nitric acid at a low temperature of -30°C to -10°C.

[The second step]

[0032] In general, the reduction of an aromatic nitro group is carried out by a process comprising catalytic reduction with hydrogen gas or sodium borohydride in the presence of a catalyst such as palladium, platinum, Raney nickel, etc., or by a process comprising chemical reduction with an acid in combination with a metal such as iron, tin, zinc, etc.

[0033] For the reduction of the nitro derivative of PF1022 substance as obtained in the above first step, it has been found that either a method of reacting said nitro derivative with hydrogen gas under atmospheric pressure in the pres-

ence of 5-10% palladium/carbon in an alcoholic solvent, or method of reacting the nitro derivative with tin and concentrated hydrochloric acid in an inert solvent such as dioxane is able to give the target aminated compound in a high yield from said nitro derivative of PF1022 substance.

[The third and fourth steps]

[0034] The aminated compound so obtained in the second step is then reacted with nitrous acid in the same manner as that for the diazonation of usual aromatic amino compounds, to produce the corresponding diazonium salt which is relatively stable. In fact, when the amino compound as obtained in the second step is treated with sodium nitrite or a lower alkyl ester of nitrous acid such as amyl nitrite, in combination with a suitable acid such as hydrochloric acid, sulfuric acid, trifluoroacetic acid, etc., added in the reaction system, nitrous acid is generated in situ, and it is further reacted easily with said amino compound so as to give the diazonium salt intended.

[0035] Then, in the fourth step, the resulting diazonium salt compound can be hydrolyzed to yield the PF1022 E substance.

1-2. Syntheses of various PF1022 derivatives from PF1022 E substance

[0036]

(A) When PF1022 E substance is used as the starting compound, certain of the compounds of the general formula (I), e.g. such a compound of formula (I) where R^1 is H and R^2 is 2-aminoethoxy group, or its similar compound where the hydrogen atom (s) of the amino group in said 2-aminoethoxy group is or are replaced by an alkyl group, is possible to be easily prepared by a process comprising three steps of chemical conversions, namely the process comprising the 1st step for cyanomethyl etherification of the phenolic hydroxyl group of PF1022 E substance, the 2nd step for reduction of the cyanomethyl group into 2-aminoethyl group and the 3rd step for N,N-dialkylation of the 2-amino group of said 2-amimoethyl group. This process is now concretely described for its 1st, 2nd and 3rd steps.

[The 1st step]

[0037] The reaction for cyanomethyl etherification of the phenolic hydroxyl group of PF1022 E substance may be carried out by reacting it with a halogenated acetonitrile, such as chloroacetonitrile, bromoacetonitrile and iodoacetonitrile in an inert organic solvent, including ethers such as ethyl ether, isopropyl ether, tetrahydrofuran (THF), 1,4-dioxane, etc., ketones such as acetone, 2-butanone etc., halogenated hydrocarbon solvent such as dichloromethane, chloroform and the like, as well as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO) and the like, in the presence of such a base, such as potassium t-butoxide, sodium hydride, potassium carbonate, sodium carbonate, and amines such as triethylamine, 1,8-diazabicyclo[5,4,0]-7-undecene, etc, which acts as a hydrogen halide scavenger. Preferably, this 1st step may be effected by the treatment with bromoacetonitrile, either in the presence of sodium hydride in tetrahydrofuran, or in the presence of potassium carbonate in acetone. Under these conditions, the reaction may proceed satisfactorily at room temperature and can give the desired cyanomethyl ether derivative in a higher yield than those when the reaction is effected under another reaction conditions.

[The 2nd step]

[0038] The cyanomethyl ether derivative obtained in the above 1st step can then be converted into the corresponding 2-aminoethyl-ether derivative easily by a catalytic reducing reaction in the presence of a catalyst such as palladium, platinum oxide and the like. As the reaction solvent, a lower alcohol such as methanol, ethanol, etc., is relatively suitable and the reaction may proceed smoothly at room temperature with a hydrogen gas under a medium pressure, to give the desired 2-aminoethyl-ether derivative in a high yield.

[The 3rd step]

[0039] The 2-aminoethyl ether derivative obtained in the above 2nd step can then be N,N-dialkylated in an inert organic solvent by a process (1) comprising treating said derivative with an alkyl halide in the presence of a base acting as a hydrogen halide scavenger, or by a process (2) comprising treating said derivative with a lower alkanal under such reduction conditions, either by a catalytic reduction with a catalyst such as palladium, platinum oxid.under a medium pressure, or by a chemical reduction with using sodium cyansborohydride or sodium borocyanide. Thereby, said derivative can be converted easily into the desired final compound. When the process (1) above is adopted, it is relatively suitable that DMF or DMSO is used as the solvent and that potassium carbonate is used as the base. For the alkyl hal-